REMARKS/ARGUMENTS

Claims 1-23 are pending. Claims 1, 2, 9, 10, and 22 have been amended. Claim 23 is newly added.

No new matter is entered by any of these amendments. For example, page 4, line 2; page 5, line 6; and page 6, line 8 of the specification discuss the controlled in vivo release of biologically active proteins. The synonym of "in vivo" is "within a living organism" as recited by claims 1, 9, 10 and 22. Regarding the support for "wherein the biodegradable preparation is in solid form outside the living organism", it can be found at, for example, paper 5, line 19; page 7, line 5; Table 2; and examples 1-3 of the specification. All the preparations of examples 1-3 are in solid form (pellets). The proper standard set by U.S. Patent Office for determining compliance with the written description requirement is "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed?". MPEP 2163.02. "The subject matter of the claim need not be described literally." *Supra*. "While there is not *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure". *Supra*. Hence, the amendment regarding "solid form outside the living organism" has clearly met the standard set by the Patent Office. As to the support for the newly added claim 23, it can be found at, for example, page 4, line 22.

Applicants therefore believe that the present application has been put in condition of allowance based on the above amendments and the following remarks. To facilitate the prosecution of the present application, Applicants would appreciate if the Examiner calls the attorney of record when he has any question or proposal regarding the present amendment.

Rejection over Dunn in view of Olson

Claims 1-22 as originally filed were rejected under 35 U.S.C. (a) as being unpatentable over Dunn et al. in view of Olson '540. Specifically, the Examiner stated that it would be obvious to one of ordinary skill to add crystalline modifiers to the vehicle of Dunn et al. to achieve the beneficial effect of controlled release in view of Olsen '540.

This rejection becomes moot now in view of the present amendment. For example, in Dunn, the polymer is placed into the animal in liquid form and cures to form the implant in-situ. Since Dunn aims to develop a polymer drug delivery system (including thermoplastic and thermosetting polymers), which can be administered as liquids via, for example, syringe and needle (see col. 2, lines 54-60), the maximum molecular weight of the polymer used by Dunn is 10,000 (see examples 10-11). Dunn discloses neither polymer delivery system, which is administered as solids, nor any polymer that has a molecular weight ranging from 15,000 to 100,000. Hence, even if a person of ordinary skill in the art would have added the crystallization modifiers of Olson '540 to the polymer delivery system of Dunn, as the Examiner proposed, he or she would still have not arrived at the present invention as claimed by any of claims 1-22.

Therefore, Applicants respectfully request the Examiner withdraw the rejection over Dunn in view of Olson '540 under 35 U.S.C. 103(a).

Rejections over Olson in view of Dunn

Claims 1-22 as originally filed were also rejected under 35 U.S.C. 103(a) as being unpatentable over Olson '540 in view of Dunn. Specifically, the Examiner stated that it would have been obvious to one of ordinary skill to deliver protein drugs in the vehicle of Olson '540 for the beneficial effect thereof in view of Dunn's teaching that such drugs are deliverable in a vehicle comprising polycaprolcatone.

Applicants respectfully traverse.

Firstly, a person of ordinary skill in the art would not be motivated to apply the protein into the polymer delivery system of Olson '540. By contrast, reading the teachings of Olson '540, there is a strong prejudice for those skilled in the art against considering Olson '540 as providing preparations containing bioactive proteins.

As described in Example 1 of the Olson '540, the composition is produced by using 9% methanol and 80% methylene chloride as organic solvents to dissolve the polycaprolactone. Further, in Example 2, the composition for the controlled release of methylene blue as a model substance requires the polycaprolactone and mono-diglycerides to be heated to about 90 °C and stirred to give homogeneous melts just prior to introducing the methylene blue. Olson '540 provides no other example.

However, it is well known for those skilled in the art that proteins outside their natural environment can be easily destroyed or inactivated so that they lose their original functionality. It is known that proteins can be inactivated in the presence of organic solvents such as 9% methanol and 80% methylene chloride used by Olson' 540. This is due to the fact that in organic solvents, proteins, e.g. enzymes, change their natural conformation because of the impact the solvent has on the groups that control protein folding. Depending on the polarity of the solvent the protein changes to different unnatural conformations. As a consequence, the natural functionality or in case of enzymes the natural catalytic potential is altered in an undesired way. Normally, enzymes are known to function effectively only in aqueous solution and become unstable and catalytically inactive in the presence of organic solvents (see also page 3, lines 15-25 of the specification of the present application). The Declaration of James Olson that was submitted with the Amendment filed April 26, 2001 in the parent application, Serial No.

10/075,184 referred in paragraph 9 to an article entitled "Why are enzymes less active in organic solvents than in water?" that discussed the drastically diminished enzymatic activity in organic solvents (A.M. Klibanov, Trends in Biotechnology, 15(3): 97-101, March, 1997).

Thus, a person of ordinary skill in the art would not expect that protein being dissolved in methanol or methylene chloride would retain its biological activity.

Furthermore, it is known, that the activity of proteins, especially larger proteins like enzymes, can be easily destroyed by subjecting them to higher temperatures. Higher temperatures normally cause an irreversible change of conformation, the so-called denaturation, e.g. during egg cooking. The critical temperature in the living world is in most cases about 40 °C. As a consequence of applying higher temperatures proteins were known to be inactivated.

Thus, a person skilled in the art would not expect that thermally sensitive protein being heated to such temperatures would retain its biological activity.

That leads to the prejudice that the methods of processing the preparations by using either organic solvent or heat according to the Olson' 540 are too harsh to preserve the activity of proteins, so those skilled in the art would not have applied the protein mentioned by Dunn to the delivery system of Olson '540.

Secondly, the combination of the teachings of Dunn and Olson' 540 is "obvious to try" at most, rather than "obvious to arrive at" the present invention for a person of ordinary skill in the art. Dunn generally lists a number of pharmaceutical agents in a long paragraph bridging cols. 6 and 7, such as antibiotics, anti-inflammatory agents, which likely encompass thousands of specific agents. However, Dunn never provides any specific instruction as to the use of which specific agent in what specific amount and under what specific conditions that would be successful.

As MPEP 2145 X (B) clearly states, "obvious to try" is an improper rationale in support of an obviousness rejection. A detailed explanation is also provided therein. For example, it cites: "The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try 'would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful....In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d 894,903, 7 U.S.P.Q. 2d 1673, 1681(Fed. Cir. 1988) (citations omitted).

Therefore, based on the facts of the present case, it is at most "obvious to try" to combine Dunn and Olson '540 to arrive at the present invention. Accordingly, the present pending claims 1-22 are not obvious over Olson '540 in view of Dunn. For the same reasons discussed above, new claim 23 is not obvious over Olson '540 in view of Dunn. Withdrawal of the obviousness rejection of the present application over Olson '540 in view of Dunn is respectfully requested.

Based on the forgoing reasons, Applicants believe that the present application is in condition of allowance. Early and favorable action is earnestly and respectively requested. A check in the amount $86 is enclosed in payment for the addition of independent claims in excess of three.

It is believed that no other fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,

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Dated: July 27, 2004